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Vitamin D Level after Allogeneic Hematopoietic Stem Cell Transplant

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Vitamin D (VD) deficiency can cause osteomalacia, bone pain, muscle weakness, fatigue, and increased risk of fracture, and may precipitate or exacerbate osteopenia and osteoporosis. Patients receiving treatment for acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) may have limited exposure to sunlight and often experience gastrointestinal side effects that may decrease their ability to maintain an adequate VD level. We hypothesized that patients with AML and ALL would have a low VD level after allogeneic hematopoietic cell transplant (HCT), and that these patients would have a high incidence of osteoporosis/osteopenia. We therefore studied the incidence of low VD level and low bone mineral density after HCT. Of 289 patients with AML or ALL undergoing HCT between January 1, 2000, and January 31, 2009, at the Cleveland Clinic, 58 (20.1%) patients had VD testing after HCT. Of these, 52 (89.7%) patients had a low VD level, and 6 (10.3%) had a normal level. Most patients with VD testing had graft-versus-host disease (GVHD) and were taking corticosteroids (94.8% and 98.3%, respectively). Of the 49 patients with VD testing who also had bone mineral density testing, 65% had abnormal (low bone density) results. Only 21% of patients with VD testing were taking VD supplements prior to testing, and 65% had an elevated parathyroid hormone level. We found that most patients did not have VD testing after HCT, but those that did were very likely to have a low level and have low bone mineral density. Those with a low VD level were likely to have received corticosteroids, have GVHD, and have an elevated parathyroid hormone (PTH) level. Given the potential morbidity of low VD level, VD deficiency should be considered after HCT. Prospective study of VD level and its impact on morbidity and mortality after HCT is warranted.

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INTRODUCTION

Vitamin D (VD) deficiency can cause osteomalacia, bone pain, muscle weakness, fatigue, and increased risk of fracture, and may precipitate or exacerbate osteopenia and osteoporosis. The health problems potentially caused by VD deficiency are not inconsequential. To maintain normal skeletal homeostasis, calcium and VD are required. VD aids in calcium absorption from the gastrointestinal tract. If VD level is low, there is decreased calcium absorption leading to a negative calcium balance. This results in a compensatory rise in parathyroid hormone (PTH), which then drives excessive bone resorption [1].

Humans attain vitamin D from exposure to sunlight, diet, or dietary supplements. Very few foods are significant sources of vitamin D without fortification (fortified foods include cereal, orange juice, and milk products). Causes of VD deficiency include reduced skin synthesis, reduced absorption of VD in the gastrointestinal tract, and inherited or acquired disorders of VD metabolism. In addition, liver failure and chronic kidney disease can cause decreased synthesis of VD, and anticonvulsants, glucocorticoids, and antirejection medications can cause increased catabolism of VD [1].

Patients presenting for allogeneic hematopoietic cell transplant (HCT) may already have a low VD level because of decreased exposure to sunlight from prolonged hospital stays, limited outdoor activity, and sunscreen use, and decreased oral intake because of gastrointestinal treatment toxicity. Current recommendations in those patients who have undergone

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HCT advise avoidance of unprotected UV exposure to reduce risk of secondary cancer [2]. Gastrointestinal graft-versus-host disease (GVHD) may further limit absorption of VD after HCT. HCT patients also receive medications that cause increased breakdown of VD, and often have impairments of renal and liver function. Thus, HCT patients are at risk for VD deficiency and the bone abnormalities that result.

It is known that osteoporosis or osteopenia is present in 49% of patients before HCT [3] and occurs in over 50% of patients after HCT [4,5]. Patients with normal bone mineral density before HCT have a statistically significant decrease in bone mineral density afterward [6]. The principal factors leading to bone loss after HCT are immunosuppressive therapy, hypogonadism, kidney dysfunction, malabsorption, radiation therapy, chemotherapy, and cytokine therapy [7,8]. VD deficiency may also play a role in bone loss, but has not been carefully studied to date in the HCT population. A case report has been published describing the impact of VD on bone density after HCT [9]. Although decreased VD intake after HCT has been demonstrated [10], VD deficiency may not be routinely suspected, and its effect on bone mineral density has not been well demonstrated in HCT patients.

The current study was undertaken to describe VD level in patients after HCT and to evaluate the incidence of osteoporosis/osteopenia among those with a low level. We hypothesized that patients with acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL) would have low VD level after HCT, and those patients with a low level would have a high incidence of low bone density. We therefore retrospectively studied VD level and bone density measurements after HCT in patients with acute leukemia to determine the incidence of low VD level and osteopenia/osteoporosis in this population. Data on corticosteroid use, diagnosis of GVHD, and PTH level was also collected.

MATERIALS AND METHODS

A total of 289 patients with AML or ALL underwent myeloblative or nonyeloablative HCT between January 1, 2000, and January 31, 2009, at the Cleveland Clinic. Patients were treated with a variety of conditioning regimens. Baseline demographic data, disease characteristics, transplant variables, and outcomes data were obtained from the transplant database, which contains prospectively collected data on all patients who underwent transplantation at our center. All patients included in this study were treated on protocols approved by the Cleveland Clinic's institutional review board (IRB) and gave signed informed consent to allow data collection. These data were supplemented by an IRB-approved retrospective chart review for posttransplant VD level, VD supplementation at the time of VD level, PTH level at the time of VD level, bone density result closest to the time of VD level (either before or after), diagnosis of GVHD, and specialty of physician ordering VD level.

OH VD levels were measured by a direct, competitive chemiluminometric immunoassay (CLIA) on the automated platform Liaison (Diasorin Inc., Vercelli, Italy). VD levels were categorized as sufficient (>30 pg/mL), insufficient (20-30 pg/mL), or deficient (<20 pg/mL). PTH levels were determined by a 2-site sandwich CLIA on the automated platform ADVIA Centaur (Siemens Corp., Deerfield, IL). PTH levels were categorized as normal (10-60 pg/mL), low (<10 pg/mL), and high (>60 pg/mL). Bone density exam was performed at the Cleveland Clinic. A total of 14 bone density scanners by Lunar and Hologic were used during the time frame of this study. These scanners were maintained with the required quality assessments and were within normal operating procedures. Each patient result was compared with the reference database for the manufacturer for diagnosis. For patients over the age of 50, the World Health Organization criteria was used to define bone density (normal bone density = T score ≥ -1.0 , osteopenia = T score < -1.0 but > -2.5, and osteoporosis = T score < -2.5 SD. For patients under the age of 50, the *Z*-score was used (*Z*-score ≤ -2 was considered abnormal bone loss). Results were recorded as normal (no osteopenia, osteoporosis, or abnormal bone loss) or abnormal (osteopenia, osteoporosis, or abnormal bone loss).

Statistical Analysis

Among 289 patients, VD testing was assessed relative to 5 variables: gender, age at transplant, diagnosis (AML or ALL), transplant type (myeloablative or reduced-intensity conditioning [RIC]), and year of transplant. The chi-square test was used to determine whether VD testing differed by gender, diagnosis, or transplant type; the Cochran-Armitage trend test was used to determine whether VD testing was associated with age or year of transplantation.

Among 58 patients whose VD level was tested, continuous variables were compared between patients with normal and low VDL using the Wilcoxon rank sum test, and categoric variables were compared using Fisher's exact test.

The incidence of low VD level and the incidence of osteoporosis/osteopenia were estimated using exact 95% binomial confidence intervals (CI) (95% CI).

Analyses were done using SAS software (SAS Institute, Inc., Cary, NC). All statistical tests were 2 sided, and $P \leq 0.05$ was used to indicate statistical significance.

RESULTS

Among 289 patients, 58 (20.1%) had VD testing post-HCT. Patients were more likely to have VD testing if they were female (27.7% versus 12.8% in males; $P = .002$) and if HCT was performed more recently ($P < .001$). The likelihood of testing did not differ between AML and ALL ($P = .14$) or between myeloablative and RIC transplants ($P = .40$). Older patients were somewhat more likely to be tested than younger patients, but this difference was not quite significant ($P = .08$). Among 58 patients with VD testing, the mean time from HCT to VD testing was 13.8 ± 18.0 months. Testing was ordered most commonly by physicians in the osteoporosis/metabolic disease clinic (79.3%) followed by the HCT physician (8.6%), women's health exam provider (3.4%), palliative medicine physician (3.4%), inpatient medicine team (1.7%), pulmonary physician (1.7%), and unknown provider (1.7%). Fifty-two (89.7%; 95% CI 78.8-96.1) patients who had VD testing had a low level, and 6 (10.3%) had a normal level. Of those with a low level, 18 were insufficient and 34 were deficient. There was no significant difference between patients with low and normal VD levels with respect to gender ($P = .16$), age at transplant ($P = .84$), diagnosis ($P = .32$), or type of transplant ($P = .0$). Patients with low VD level were transplanted more recently than those with normal VDL (median 2006 versus 2004; $P = .038$). Most patients with VD testing had GVHD and were taking corticosteroids (94.8% and 98.3%, respectively). Only 21% of the patients with VD testing were taking VD supplements prior to testing. Of the 49 patients with VD testing who also had bone density testing, 65% (95% CI 50.4-78.3%) had abnormal scans. PTH level was assessed in 38 (66%) of the patients who had VD testing done. Of those who had PTH level, 26 (68%) had an abnormal result. All but 1 of the abnormal PTH levels were high. Patient demographics are noted in Table 1.

Table 1. Patient Demographics

Variable	N	%
Gender		
Female	39	67.2
Male	19	32.8
Age at transplant, years		
Mean ± SD	45 ± 13	
Median (range)	47 (18-66)	
Diagnosis		
AML	47	81.0
ALL	11	19.0
Type of transplant		
Myeloablative	50	86.2
Nonmyeloablative	8	13.8
Conditioning regimen		
Bu/Cy	28	48.3
TBI/VP	12	20.7
TBI/Flu	8	13.8
Bu/Cy/VP	5	8.6
TBI/Cy	3	5.2
TBI/Cy/ECP	1	1.7
TBI/VP/ATG	1	1.7
Donor		
Related	31	43.4
Unrelated	27	46.6
Months from transplant to first VD level		
Mean ± S.D.	13.8 ± 18.0	
Median (range)	5.9 (0.7-90.4)	
Taking VD supplement at time of first VD level		
Yes	12	20.7
No	46	79.3

N indicates number of patients; SD, standard deviation; AML, acute myeloid leukemia; ALL, acute lymphoblastic lymphoma; Bu, busulfan; Cy, cyclophosphamide; TBI, total-body irradiation; VP, etoposide; Flu, fludarabine; ECP, extracorporeal photopheresis; ATG, antithymocyte globulin; VD, vitamin D.
N total =58 patients in whom vitamin D level was assessed.

DISCUSSION

Morbidity and mortality is a significant limitation of HCT. Identification of correctable factors, such as VD deficiency, that could positively impact outcome are needed. It is known that HCT patients do not ingest adequate VD [10], are advised to avoid sun exposure [2], receive immunosuppressive medication, and can have organ system compromise. Despite having these risk factors for VD deficiency, HCT patients are not often routinely screened with VD level or routinely advised to take VD supplements.

In this study only 20% of HCT patients had VD level assessed, although 90% the patients tested had a low level. Only 12% of the patients who had a VD level assessed were taking VD supplements. This suggests that though VD deficiency may not be routinely suspected in HCT patients, it should be considered and assessed. Whether HCT patients should routinely be placed on a VD supplement is not known. Even healthy individuals living in areas with low sun exposure require approximately 800-1000 IU of VD daily to maintain an adequate level [1]. (Although VD level can vary by time of year, because of limited sun exposure in Cleveland, Ohio, VD levels were not compared by date of assessment.) The high incidence of low VD level in those tested supports further investigation of VD level in all HCT patients, and the assessment of VD level in all patients who have used corticosteroids or have a history of GVHD.

The retrospective data presented in this article supports a small prospective study by Massenkeil and colleagues [3] who demonstrated low VD levels after HCT. Their study was conducted to primarily assess bone mineral density after transplant, but the VD findings were significant. Sixty-seven patients were prospectively evaluated for radiologic and biochemical changes in bone metabolism with the goal to better define risk groups for osteoporosis after HCT. They found that 26/53 (49%) of patients had decreased bone density before HCT. All patients after HCT

had a decline in bone density. VD levels were low in 22/57 (39%) of patients before HCT, and all patients had low VD level up to 6 months after HCT. The current study noted that those patients with a low VD level were likely to have a low bone density. VD deficiency predisposes patients to a variety of potential health problems including osteoporosis, which is already a known complication of HCT. Whether supplementing VD in HCT patients could have prevented this bone loss can by hypothesized, but it is not known.

Low VD level, corticosteroids, abnormal bone density exam, and elevated PTH level all independently predict for bone health problems. Most patients in this study who had a PTH level assessed had a high level. PTH elevation can be caused by VD deficiency, renal failure, and loop diuretics. It cannot be determined from this study whether elevated PTH level was secondary to VD deficiency. VD deficiency could be secondary to elevated PTH caused by renal insufficiency or iatrogenic diuretics used during transplantation. Prospective assessment of VD level and PTH level throughout transplantation would elucidate the underlying cause of low VD level and elevated PTH.

Providers other than the HCT physician were the most likely to check VD level. Testing was ordered most commonly by physicians in the osteoporosis/metabolic disease clinic. The Cleveland Clinic has a bone and metabolic disease clinic for patients who have or are at risk for low bone density, and HCT patients are frequently referred there for evaluation. The reason for referral to this clinic was most likely recognition of high risk for osteoporosis because of corticosteroid use (98% of patients with VD level have received corticosteroids). The retrospective nature of our data prohibits determination of referral source and reason for referral to this clinic, but it is likely that it was the HCT physician. This would imply that though the HCT physicians were not the most likely to test VD level, they were adequately evaluating the bone health of patients after HCT by referring them to an appropriate subspecialist. Patients were also more likely to have VD testing if their HCT was done in more recent years. Practitioners may currently be more aware of the role VD plays in bone health than in previous years as VD in now being recognized to have multisystem effects.

This study was designed to define the incidence of low VD level after HCT and describe the bone health in those patients tested. VD supplementation may have other benefits beyond improving bone health after HCT. VD levels have been correlated with cancer incidence and prevention [11]. Vitamin D metabolites have been studied for use in the treatment of myeloid leukemia in older adults [12] and relapsed AML [13]. VD also activates the up-regulation of human cathelicidin, which has antimicrobial as well as antiendotoxin activity. Thus, it has been hypothesized that maintaining adequate VD level may reduce the incidence and improve the prognosis in septicemia [14]. A recent study has shown that VD insufficiency in patients with non-Hodgkin lymphoma was associated with inferior event-free survival and overall survival [15]. Vitamin D may be a factor that plays a more pivotal role than only modulating bone health. Via its relationship to PTH, cellular differentiation, proliferation, and angiogenesis, it could potentially be a key factor in advancing the practice of HCT [16].

Our study confirms a high incidence of VD deficiency after HCT in acute leukemia patients with GVHD who have taken corticosteroids. These patients are at risk for low bone density and osteoporotic bone fracture, and often complain of bone pain, muscle weakness, and fatigue that may be amenable to VD supplementation. VD supplementation may be a low cost, easy to implement addition to routine care after HCT that might increase quality of life and reduce HCT-associated morbidity. Further prospective study of VD and its impact in HCT is warranted.

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